addressing the regulation of functional foods. 'Functional foods' is a concept that everyone knows about but for which there is no official policy. The FDA must face the issues raised by these products to ensure that functional foods become a public health boon rather than the snake oil of the 21st century."

Estrogen's a Natural in Herbal Remedies

Patricia Eagon, an associate professor of medicine at Pennsylvania's University of Pittsburgh, decided to consult an herbalist after she began to suspect that Premarin, the prescription estrogen she was taking for menopausal symptoms, was causing a rash on her leg. The herbalist, whom she had consulted before on other health matters, gave her a mixture of several herbs to take instead of Premarin. The concoction both relieved Eagon's hot flashes and piqued her curiosity about how the herbal ingredients worked.

Eagon decided to launch her own experiment to find out. She conducted an estrogen-binding assay on 15 herbs commonly used in treating menopause, including 3 from the remedy she had taken herself. Herbs that showed estrogenic activity in the screening were then fed to rats that had undergone ovariectomy. To test the herbs' estrogenicity, Eagon weighed the rats' uteri at the end of the study and measured changes in the concentration of luteinizing hormone in their blood (enlarged uterus and decreased luteinizing hormone concentration are both indicators of estrogenic activity). The tests indicated an estrogenic effect in four of the herbs—chaste tree berry (*Vitex agnus-castus*), dong quai (*Angelica sinensis*), American ginseng (*Panax quinquefolium*), and black cohosh (*Cimicifuga racemosa*). Eagon reported her findings on 11 April 1999 at the annual meeting of the American Association for Cancer Research and is currently preparing the results for publication.

Eagon's findings have implications for the fast-growing number of people who are embracing alternative medicine. According to the U.S. Food and Drug Administration (FDA), more than half of all U.S. adults use over-the-counter vitamins, dietary supplements, or herbal remedies. Ann Fonfa, founder of the New York City–based Annie Appleseed Project to promote the study of alternative cancer treatments, estimates (based on national averages for the general population) that 30% of menopausal women treat themselves with medicinal herbs, many because they believe such herbs are safer and gentler than prescription drugs. Yet they have no proof of the herbs' medicinal value and safety beyond the folk wisdom of herbalists; unlike pharmaceutical manufacturers, manufacturers of herbal remedies are not required by the FDA to prove their products' safety and efficacy.

Eagon's discovery of estrogenicity in the herbs she tested comes as no surprise to some researchers. "While the specific findings are new, there is well-known, well-described estrogenic activity in plants," says Daniel Sheehan, director of the Endocrine Disruptor Knowledge Base Program of the FDA's National Center for Toxicology Research in Jefferson, Arkansas. He points to the example of subterranean clover, a type of clover that farmers have known for 50 years to cause reproductive failure in sheep.

While Eagon's research may help explain why certain herbs may relieve hot flashes and other menopausal symptoms, it raises several more questions. Of key interest is how these phytoestrogens react in the body. "We really need to measure these things in women," Eagon says.

Laura J. Stafford

Herbal estrogens. A recent study by associate professor of medicine Patricia Eagon suggests that some herbs may have powerful estrogenic properties.

Premarin has long been doctors' drug of choice in treating menopause because it not only relieves symptoms but also helps prevent osteoporosis and heart disease. However, the synthetic hormone also elevates women's risk of breast and uterine cancer, which scares many would-be users away.

Because of the estrogenic activity she observed in the herbs she studied, Eagon feels compelled to warn women at high risk of breast or uterine cancer against taking them, as estrogen has been implicated in some forms of cancer. Yet she admits she doesn't know if the herbs promote cancer. In fact, she says, "We may test these further and find they inhibit cancer. It looks as if soy has a positive effect in preventing breast cancer. These herbs may also be able to prevent it."

Eagon also doesn't know if estrogenic herbs give women the same protection against heart disease and osteoporosis that synthetic estrogen does. "One question is, how do estrogenic substances from plants compare in activity with pharmaceutical estrogens," says Fredi Kronenberg, director of the Rosenthal Center for Complementary and Alternative Medicine at Columbia University College of Physicians and Surgeons in New York City. "Do they have a broad spectrum of estrogenic activity or are they more selective in action? We don't have the answer yet."

Some of those answers may come out of Eagon's upcoming research. She first plans to investigate whether the herbs inhibit or promote breast cancer by feeding them to rats with a genetic susceptibility to the disease. Eagon also plans to delve into the herbs' effects on premenopausal women. Younger women take chaste tree berry and dong quai for premenstrual syndrome, amenorrhea, and infertility; American ginseng is recommended for stomach upset, lack of appetite, physical exhaustion, and infection. Eagon would use mice with intact ovaries to simulate the impact on premenopausal women.

"People think [taking herbal remedies] is like eating another serving of broccoli," Eagon says. "These things are not all benign. The more we know about them, the better off we'll be."

Harvesting Monoclonal Antibodies from Plants

When monoclonal antibodies were first developed 20 years ago, they were hyped as a magic bullet for curing cancer and other diseases. However, killing cancer cells with these immune proteins, which are artificially produced and which neutralize one specific antigen or foreign protein, was not as straightforward as first assumed, and clinical failures occurred. Moreover, the high cost of producing monoclonal antibodies by traditional cell fermentation methods limited their applications. These setbacks have forced scientists to look more realistically at monoclonal antibodies.

Now, researchers at EPIcyte Pharmaceutical, based in San Diego, California, hope to revitalize interest in monoclonal antibodies with a new technology that produces large supplies of the proteins inexpensively. Their new technology uses green

plants to churn out large quantities of "plantibodies." After undergoing some genetic engineering, plant cells easily assemble monoclonal antibodies. Plants are expected to be able to make unlimited quantities of plantibodies at prices that will be 25–100 times less expensive than cell fermentation methods.

The current standard cell fermentation methods can produce just 5–10 kg of a monoclonal antibody in a year. In comparison, EPIcyte plans to produce 10,000 kg of key plantibodies per year. The current high cost of monoclonal antibodies, which ranges from $200 to $1,000 per gram, is predicted to fall to $10–100 per gram or less as plants produce tons of plantibodies.

A large, cheap supply means that new medical, consumer, and industrial applications for monoclonal antibodies could become economically feasible. For instance, plantibodies could target toxicants or pollutants in large-scale water purification systems, theorizes biochemist Andrew Hiatt, a developer of plantibodies who cofounded EPIcyte in 1996 along with plant physiologist Mich Hein. Plantibodies that sequester heavy metals or radioactive compounds could become tools for bioremediation.

The first plantibodies were produced in tobacco plants, but to meet commercial demands, EPIcyte is developing corn that produces monoclonal antibodies. Corn is the most widely grown crop worldwide, and its seed (kernel) naturally stores plantibodies in a low-moisture environment that is loaded with protective protease inhibitors. Stored plantibodies can be purified as needed by standard milling procedures. The high-molecular-weight (300,000–400,000 daltons) plantibodies easily separate from the low-molecular-weight (< 50,000 daltons) corn proteins when solubilized.

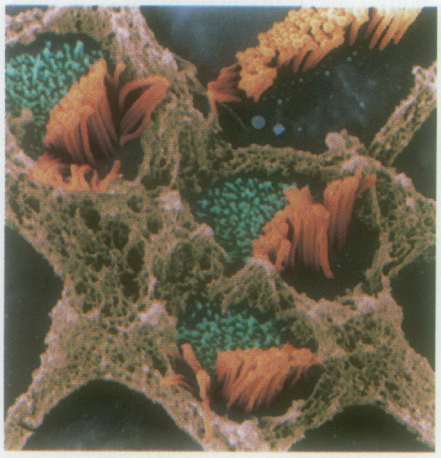
The first clinical evidence of plantibodies' effectiveness appeared at Guy's Hospital in London. A plantibody against *Streptococcus mutans*, which produces lactic acid and erodes tooth enamel, was produced in tobacco plants. When brushed onto human teeth for three weeks, the plantibody prevented tooth decay for up to four months, as described in the May 1998 issue of *Nature Medicine*. The plantibody "specifically inhibits *Streptococcus* from binding to tooth surfaces," says Hiatt.

EPIcyte holds exclusive license for plantibody technology from The Scripps Research Institute in La Jolla, California. In alliance with ReProtect of Baltimore, Maryland, EPIcyte is developing preclinical topical gels that contain plantibodies for herpesvirus types 1 and 2. In a study published in the December 1998 issue of *Nature Biotechnology*, scientists at ReProtect applied an experimental plantibody to the vaginas of mice, which prevented infection with genital herpes. EPIcyte and ReProtect scientists are planning a joint project to make a more potent herpes plantibody to protect newborn babies against transmission of herpes from infected mothers during delivery.

"The greatest potential for monoclonal antibodies lies in prevention," says Kevin Whaley, a reproductive biologist at The Johns Hopkins University in Baltimore who also works for ReProtect. From a public health perspective, plantibodies are ideally suited for preventing sexually transmitted diseases as over-the-counter products. More than 5 million people in the United States are infected with sexually transmitted diseases annually at an estimated cost of $12 billion in medical treatment. Whaley says, "[Monoclonal] antibodies are so potent and so specific, they can be used in novel ways," such as personal lubricants, gels, or controlled-release devices for vaginal insertion. To accommodate personal preferences, several different user-friendly formulations for plantibodies will be developed, says Whaley.

All Ears: Potential Help for Noise-Induced Hearing Loss

Two separate teams recently published findings that may help prevent or reduce noise-induced hearing loss, the most common form of hearing loss. According to the American Academy of Otolaryngology, an estimated 16–24 million people in the United States have some amount of hearing loss due to sensory hair cell loss. Hair-cell loss can be caused by overexposure to loud noise, ototoxic drugs (including some antibiotics and anticancer drugs), disease, genetic factors, and simple aging. Experts generally agree that continuous noise levels over 80 decibels, or about the loudness of a busy city street, can be hazardous to hearing.



Edwin W. Rubel, Dale Cunningham

Bird's-ear view. Studying normal and regenerating hair cells in birds may help researchers find answers to hearing loss in humans.

The cochlea, a bony, coiled, fluid-filled structure of the inner ear, is lined with an epithelial layer called the organ of Corti. This organ is lined with microscopic hair cells that translate sound waves into nerve impulses that are sent to the brain. Loud noises can overstimulate and subsequently kill these hair cells. Once the hair cells are damaged, the ear can no longer transmit sound to the brain. Although birds can regenerate damaged hair cells, humans cannot; lost hair cells mean permanent hearing loss.

Richard J. Salvi, a professor of communicative disorders and sciences at the University of Buffalo in New York, and colleagues Alfred Stracher and Abraham Shulman, both of the State University of New York Health Science Center in Brooklyn, have discovered that a compound called leupeptin may protect against noise-induced hearing loss by preventing the loss of hair cells. The study was published in the 17 March 1999 issue of *NeuroReport*.

The scientists infused the right cochleae of several chinchillas with leupeptin for 14 days, while the left cochleae were left untreated as a control. The chinchillas were exposed to noise at either 100 or 105 decibels for 48 hours. The scientists found that the untreated cochleae lost massive amounts of hair, ranging from nearly 100% in the basal portion to about 15% in the uppermost portions. Conversely, the treated cochleae retained all but a few hairs. Overall, leupeptin reduced the loss of outer hair cells—the cells that are first damaged by noise—by an average of 60%.

The study was based on the premise that exposure to loud noises causes an increased production of calcium in nerve cells. This starts a chain of events that eventually leads to nerve degeneration. Leupeptin is one of a family of peptides that have been shown to short-circuit this chain of events. It is not clear, however, exactly how leupeptin works to protect the hair cells.

In a companion study, the scientists found that leupeptin didn't protect against the ototoxic effects of the anticancer drug carboplatin, possibly due to the mechanism by which carboplatin causes hearing damage. But Salvi is not discouraged; on the contrary, he believes leupeptin or a similar compound may yet be useful against the effects of ototoxic drugs. "We hope compounds like this will have some therapeutic value, perhaps provide protection against carboplatin or cisplatin [another anticancer drug]" he says, adding that such compounds could be used in tandem with ototoxic drugs.